Final Action Cover Sheet
Bristol-Myers Squibb Position Paper
Comments on Regulatory Actions

Name of Regulation/Guidance: "Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis – Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation"		
Type of Submission:		
To PhRMA	X	PhRMA Comment Due Date: Not applicable.
To FDA	X	FDA Comment Due Date: March 31, 1999
Overview/Summary: This draft guidance was published on November 30,1998 (Docket No. 98D-0994; Federal Register, Vol. 63, No. 229) to solicit comments from industry. It applies to sponsors of NDA's, ANDA's, NADA's, ANADA's, DMF's, and VMF's who intend to make postapproval changes in site of manufacture, scale of manufacture, equipment, specifications, and/or process for intermediates in the synthetic pathway leading to a drug substance. Postapproval changes involving the drug substance are not addressed by BACPAC I; but will be in a subsequent guidance (BACPAC II). Key concepts in the draft guidance are: 1) The dividing line between BACPAC I and BACPAC II is "the final intermediate". This is a new term that is defined in the BACPAC I guidance. 2) Manufacturers must examine impurity profiles and physical attributes to demonstrate equivalency of material produced before and after a change. Evaluation proceeds sequentially, starting with the synthesis intermediate directly involved in the change; then subsequent intermediate(s); and/or the drug substance. If equivalence of intermediates is proven, there is no need to test the drug substance. 3) Equivalency is assessed in relation to historical test results, rather than specifications. 4) Certain types of changes may be reported to FDA in an NDA annual report or a "Changes Being Effected" supplement, rather than by a "Prior Approval" supplement.		
Request:		
Return to:		Return By (date):
Approved By: Robert L Simon		Not Approved By:
Date Approved: 3/8/99		Date Rejected:
If not approved, please explain:		
Other Comments:		

98D-0994

C31

DATE

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 98D-0994; "Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis – Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation", *(Federal Register, Vol. 63, No. 229, November 30,1998)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on FDA's draft guidance for industry: "BACPAC I Intermediates in Drug Substance Synthesis – Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation".

We commend the U.S. Food and Drug Agency for:

1.) Seeking to reduce the regulatory burden on the pharmaceutical industry with regard to filing and/or reporting post approval changes in the synthesis of drug substances and drug substance intermediates.

2.) Recognizing that drug substance regulations and guidances must take into account the essential differences between:
- Synthetic and semi-synthetic drug substances versus drugs derived from natural sources.
- Changes involving a drug substance versus a drug product.
- Changes involving a drug substance intermediate versus a drug substance.

3.) Incorporating into the BACPAC I document the concepts that :
- Changes involving early synthesis intermediates have less potential for adverse impact on the drug substance, and consequently on the finished drug product.
- Certain types of changes (such as equipment or manufacturing site) are less likely to result in adverse effects than others (such as a change in synthesis route).

4.) Providing regulatory relief by not requiring :
- FDA notification for use of equipment not significantly different from that previously used.
- FDA notification for site changes within the same facility.
- Submission of stability data or a stability commitment in support of BACPAC I changes.

5.) Addressing the issue of redefining "isolated synthesis intermediates" as "starting materials".

However, there are several aspects of the proposed guidance that we believe require change or clarification, which are cited below. In accord with FDA's instructions, our comments are keyed to the corresponding line number(s) assigned to the text of the BACPAC I draft guidance. Where appropriate, portions of the guidance are quoted for ease of reference.

1.) Lines 11 – 13 : "It *(the BACPAC I guidance)* is limited to structurally well-characterized drug substances for which impurities can be monitored at the levels recommended".

• Many "old" drugs and their synthesis intermediates are not well characterized in terms of impurity profile. Therefore, for changes involving a synthesis intermediate (other than the "final intermediate"), it is recommended that alternatively, equivalence be demonstrated by testing material manufactured following a change for compliance with the filed, FDA-approved specifications; provided those specifications adequately define all requisite attributes of the compound.

• It is recommended that the word "structurally" be removed, since it is superfluous. An approved drug substance is by definition a material whose chemical structure is known.

2.) Lines 35 - 39 : "This guidance provides for less burdensome notice of certain postapproval changes within the meaning of paragraph 314.70(a). For changes filed as a *changes being effected* supplement [21 CFR 314.70(c) and 514.8(d)(3)], the FDA may, after a review of the supplemental information, decide that the changes are not approvable."

• It is recommended that the FDA review the nature and content of the "Changes Being Effected" supplement prior to assigning a supplement number. This approach would be similar to SUPAC. If the overall content meets BACPAC I requirements, then a supplement number would be assigned and sent to the sponsor, indicating acceptance of the supplement as a BACPAC submission and enabling implementation of the change. Submission review and approval would still be required by FDA. In addition, a facility would be considered to have a satisfactory cGMP status, if during the last FDA inspection, a recommendation was made for facility approval which related to similar technology and quality systems. These criteria would eliminate any uncertainty related to the optimal use of BACPAC I.

3.) Line 69 - 71 : "The synthesis of the drug substance should have been fully described, from starting materials to final drug substance, either in a drug application or in one or more master files."

• It is recommended that this sentence be reworded to read: "The synthesis should have been fully described in an approved application, or in one or more Drug Master Files."

4.) Lines 92 - 96 : "Two major factors for determining equivalence in the drug substance are the impurity profile and physical properties. For the purposes of this guidance, only these factors will

be considered. However, other factors that may be important in individual cases should be evaluated to demonstrate equivalence. For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change."

• We agree that impurity profile and physical properties are the major factors for determining drug substance equivalence. However, in cases where a drug substance has more than one isomer and bioequivalence of these isomers has been previously demonstrated, it is unnecessary that the identical quantitative mixture be obtained after the change. We recommend this be clarified in the BACPAC I guidance.

5.) Lines 123 - 124 : The general considerations for determination of equivalency of impurity profiles for isolated intermediates and drug substances require that: "...The level of impurities should be assessed by comparing 3 post-modification batches to the range of historical data from 10 pre-modification commercial batches". The BACPAC I glossary (Lines 589 – 591) defines historical data as: "Data on impurities or physical attributes from 10 recent batches representative of the established process. The upper statistical limit of an impurity is generally based on the mean plus three times the standard deviation."

• We agree that following a change, the impurity profile of the isolated intermediate, or a subsequent intermediate, or the drug substance should be assessed. However, comparison should be made against the filed, FDA-approved specifications for that material (rather than historical data). This recommendation is based on two considerations:

1) Historical data may not be available for 10 commercial batches. This is particularly true for low sales volume products, orphan drugs, and recently approved new molecular entities.

2) The specifications for an isolated intermediate are established by a manufacturer after careful consideration of the attributes of material produced by the process, and the designed capabilities of subsequent synthesis steps. Although a change may produce material with a higher impurity level, this is not significant provided the material complies with specification requirements; or the impurity is purged to acceptable levels in subsequent synthesis steps.

6.) Line 132 : A requirement for demonstration of impurity profile equivalency of an isolated intermediate manufactured following a change is: "No new impurity is observed at or above 0.1%."

• Since process-related impurities in isolated intermediates usually are purged by downstream processing, it is recommended that the BACPAC I requirement be reworded to indicate that an isolated intermediate may have a new impurity above 0.1%, provided it is removed by downstream processing, such that the impurity (or its derivative) is at or below 0.1% in a subsequent isolated intermediate or the drug substance.

7.) Line 137 – 138 : A requirement for demonstration of equivalency of impurity profile of an isolated intermediate manufactured following a change is that: "Existing impurities, including residual solvents, are at or below the upper statistical limit of historical data."

• Please see comments for lines 123 – 124 and line 132.

8.) Line 149 - 151 : A requirement for demonstration of equivalency of impurity profile of a drug substance manufactured following a change is that: "Existing impurities, including residual solvents,

are within the stated limits, or if not specified, are at or below the upper statistical limit of historical data."

• Please see comment for lines 123 – 124.

9.) Lines 156 – 158 : The guidance states the additional principle that: "Equivalence of the impurity profile may be established by testing any isolated intermediate following the change, including the final intermediate, or the drug substance."

• This statement is redundant. It duplicates the general concepts expressed in lines 109 – 117.

10.) Lines 167 – 172 : The guidance states the "additional principle" that: "Changes in process, specifications or equipment may be evaluated using data from pilot scale batches. If equivalence is demonstrated by using pilot batches, the first commercial batch should also be evaluated for equivalence. The resulting commercial batch data should be kept on file at the manufacturing site. When equivalence cannot be demonstrated at commercial scale, the reviewing division should be contacted". The term "pilot scale" is defined in the guidance as: "The manufacture of a bulk drug substance or intermediate on a reduced scale by processes representative of and simulating that to be applied on a larger, commercial manufacturing scale".

• We agree that data from pilot scale batches is supportive and can be used to determine equivalency following a change. However, the BACPAC I definition of "pilot scale" is subjective, and should be revised. According to SUPAC IR, pilot batch scale is "generally taken to be, at a minimum, one-tenth that of full production". This is a less subjective definition.

11.) Lines 173 – 177 : The guidance states the "additional principle" that: "Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with pre-change material after the final intermediate are not covered under BACPAC I. However, modified purification procedures prior to the final intermediate can be filed under BACPAC I ..."

• It is recommended that the above paragraph be reworded to indicate that an isolated intermediate (including the final intermediate) may be reprocessed by repeating a step. Reprocessing is allowed under the current GMP's based on a manufacturers intent to bring a material into compliance with specifications. Examples of processing steps that may regularly require repetition are: vacuum distillation to remove entrapped water, thermal drying to reduce solvent level, and milling to produce an appropriate particle size distribution.

12.) Lines 217 - 221 : The guidance states that: "Site changes consist of changes in location of the site of manufacture of intermediates, including the final intermediate, for both company-owned and contract manufacturing facilities. The new site, which may be within a single facility, within a contiguous campus, or in a different campus, should have similar environmental controls."

• It is recommended that definitions be included in the BACPAC I glossary for: "single facility", "contiguous campus", "different campus", and "environmental controls".

• It is recommended that the definition for "environmental controls" distinguish between controls for HVAC; controls for closed systems (equipment trains); and controls related to emissions and

wastes generated by the facility. The definition should consider that:
- The facility must maintain process conditions appropriate to the specific material, such that the process routinely produces material meeting all specification requirements.
- HVAC controls may be irrelevant, such as for a material processed within a closed system.
- Emission controls will differ from one facility to another, since each must comply with environmental requirements specific to its location (e.g. municipality, city, state and country requirements).

13.) Lines 266 - 272 : In relation to a "site change" involving an intermediate, the guidance requires submission of a Changes Being Effected supplement if: ...."The site change involves the final intermediate; or the new site is owned by a contract manufacturer not previously approved for this application; or the new site is owned by a contract manufacturer approved for this application but not approved for the step(s) being transferred."

• It is recommended that this statement be reworded to read: A Changes Being Effected Supplement is required if: "The site change involves the final intermediate, or the new site is owned by a contract manufacturer not previously approved in the application for the synthesis step being transferred. It is not necessary to notify the FDA about a site change within an approved facility."

14.) Lines 279 – 280 and Lines 307 - 308 : These lines establish the procedure for notifying FDA about a change in "scale of a manufacturing process".

• The statements are contradictory - one requires the submission of a Changes Being Effected supplement, while the other requires notification via the annual report. It is recommended that notification be done via the annual report, which is current practice.

15.) Lines 331 and Line 337 : These lines establish the procedure for notifying FDA about a change in material specifications "made to comply with compendial changes".

• The statements are contradictory - one requires the submission of a Changes Being Effected supplement, while the other requires notification via the annual report. It is recommended that notification be done via the annual report, which is current practice. Requiring submission of a "Changes Being Effected" supplement contradicts FDAMA's intention to reduce the regulatory burden placed on the pharmaceutical industry.

16.) Line 333 : The guidance requires submission of validation data for analytical test methods "revised or implemented in response to a change made by a compendia".

• Compendial methods applicable to a specific compound or solvent are validated prior to being issued as an official method. Therefore, it is unnecessary for the user to validate them again. However, if a user applies the compendial method to a non-compendial (i.e.: proprietary) compound, suitability of such application should be confirmed, and data retained at the facility for FDA review during routine cGMP compliance inspection.

17.) Lines 344 and Line 353 : These lines establish the procedure for notifying FDA about a change in material specifications that "provides greater assurance of quality".

• The statements are contradictory - one requires the submission of a Changes Being Effected supplement, while the other requires notification via the annual report. It is recommended that notification be done via the annual report, which is current practice. Requiring submission of a "Changes Being Effected" supplement contradicts FDAMA's intention to reduce the regulatory burden placed on the pharmaceutical industry.

18.) Lines 354 - 398 : These lines establish the procedure for notifying FDA about "other specification changes" such as : relaxing acceptance criteria; deleting a test; replacing an analytical method; or revising specifications in conjunction with a change in supplier/grade of starting materials, reagents, or solvents. Notification is by submission of a "Changes Being Effected " supplement.

• We agree that a Changes Being Effected supplement is appropriate for the above types of changes, with exception of a change to establish an alternate analytical method. For this type of change, it is recommended that notification be done via the annual report, which is current practice. The report should include: a material specification revised to add the new analytical method; the new method; and a validation demonstrating equivalence of the old and new methods.

19.) Lines 370 – 377 : In relation to "other specification changes", the guidance requires submission of impurity profile and physical properties data for "at least 3 batches of an intermediate made using material that justifies the revised specification(s), historical data for comparison, ...and validation data for new test methods, and existing methods."

• We agree that such evaluation is appropriate for changes involving the drug substance, but not for a synthesis intermediate. In particular, re-validation of existing test methods may not be warranted.

20.) Lines 408 - 409 and Lines 441 - 442 : These lines establish the procedure for notifying FDA about changes in the manufacturing process that: "do not involve new starting materials or intermediates".

• The statements are contradictory - one requires the submission of a Changes Being Effected supplement, while the other requires notification via the annual report. It is recommended that notification be done via the annual report, which is current practice.

21.) Lines 422 – 427 : The guidance states that: "When a new solvent is introduced into the synthetic process *(for an intermediate)* the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. The level of the new solvent in the drug substance should be below its ICH Q3C Option I limit. If the level of the new solvent in an intermediate is at or below the ICH Q3C Option I, no testing of the drug substance is needed."

• We concur with the above concept, but recommend also allowing assessment of residual solvent level according to ICH Q3C Option 2. This option permits a higher level of a solvent in a drug substance, provided the total daily exposure of a patient to that solvent from all components of the drug product is less than the pharmaceutically acceptable intake level established in ICH Q3C.

22.) Lines 461 – 466 : Please refer to comment for lines 422 – 427.

23.) Lines 503 – 506 : In relation to a manufacturer redefining an intermediate (other than the final intermediate) as a "starting material", the guidance requires submission of : "an outline of the change control protocol that has been or will be followed when establishing the suitability of a new supplier or when the existing suppliers process is changed".

• It is recommended that this requirement be removed from the guidance, since vendor qualification and change control are cGMP compliance issues. Information about vendor qualification and change control should be retained at the manufacturing facility for examination by FDA during routine facility compliance inspections.

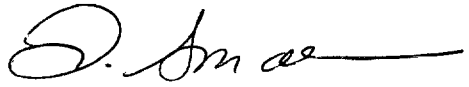
24.) Lines 580 – 584 : The guidance introduces the term "the final intermediate", and makes it the dividing line between BACPAC I and BACPAC II. The final intermediate is defined as: "...the last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance must involve covalent bond formation; ionic bond formation (i.e. making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate."

• The above definition is unsatisfactory in that it implies a drug substance synthesis has only one "final intermediate". The definition is satisfactory only when the last step is simple (such as hydrogenation or hydrolysis). However, many syntheses may for example require coupling of a side-chain and a nucleus to form the drug substance. In this case, there are two final intermediates, each of which is incorporated into the structure of the drug substance by covalent bond formation. Therefore, it is recommended that the definition be revised to indicate that a given synthesis may have more than one "final intermediate"

Bristol-Myers Squibb appreciates the opportunity to provide comments to FDA on the draft BACPAC I guidance and respectfully requests that the Agency give consideration to our recommendations.

We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Laurie F. Smaldone
Senior Vice President
Worldwide Regulatory Affairs

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